IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Karouzakis et al.	Atty Dkt: 1581/128
Serial No:	09/762,602	Examiner: Hui,S.
Date Filed:	3/21/01	Group No: 1617
Invention:	Use of Misoprostol or/and Misoprostol acid for preparing drug in order to cure sexual dysfunction in women.	Date: October 23, 2001

CERTIFICATE OF MAILING

I hereby certify that this correspondence addressed to the Commissioner for Patents, Washington, D.C. 20231 is being deposited with the United States Postal Service as first class mail on October 23, 2001.

Harriet M. Strimpel, D. Phil

Commissioner for Patents
Washington, DC 20231

DECLARATION IN SUPPORT OF APPLICANTS' RESPONSE

[37 C.F.R. SECTION 1.132]

Dear Sir:

In support of the accompanying response to the May 23, 2001 office action in the above-referenced matter, I hereby declare as follows:

1. My name is Spiros Fotinos. I am Executive Vice President of Corporate Research and Innovation at Lavipharm SA and I am familiar with the work of Drs. Karouzakis and Kanakaris described and claimed in the present patent application for treating sexual dysfunction in women. My further qualifications are listed on the curriculum vitae attached hereto as Exhibit A, which is incorporated herein by reference.

2. I have reviewed the office action dated May 23, 2001, in the above matter and have considered the statement by the Examiner that it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a topical female sexual dysfunction treating composition of misoprostol with or without another vasodilator onto the vagina or clitoris. I respectfully disagree with the Examiner.

3. Drs. Karouzakis and Kanakaris have identified for the first time that misoprostol could provide an especially beneficial effect to women when applied topically. This finding was novel and non-obvious and very exciting. The prior art described a wide range of active agents other than prostaglandins for treating men and when prostaglandins were used, the preferred form was natural PGE_1 or alpostradil, the corresponding synthetic analog. Drs. Karouzakis and Kanakaris have identified for the first time the useful properties of misoprostol for topical application. They have exploited these properties in order to prepare an effective topical formulation for treating women. These properties include (1) hydrophilicity of misoprostol which facilitates its formulation in the absence of organic solvents that act as irritants, and (2) its ability to permeate through skin and mucosa to reach target tissue.

4. Where the cited references describe the use of prostaglandins, they invariably indicate a preference for PGE_1/alpostradil. In contrast, Drs. Karouzakis and Kanakaris and his colleagues showed in addition to their studies on women, that for men, the pharmacological activity of topically applied misoprostol was substantially superior to other prostaglandins in particular, alpostradil when topically applied. (see Appendix B)

5. Moreover, the inferior activity of alpostradil as the primary agent in a topical formulation compared to misoprostol is underscored by the disappointing results reported by MachroChem for Topiglan (a topical alpostradil formulation) in men (see Exhibit C).

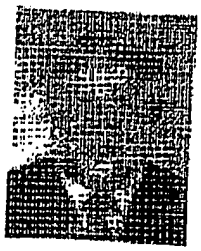
6. I hereby declare that all statements made herein of my own knowledge and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

S. Fotinos

Dated: October 23, 2001

01581/00128 178082.1

Exhibit A



SPYRIDON A. FOTINOS
Ex. Vice President - Corporate Research & Innovation

Born in Athens on 1946
He studied Pharmaceutics at the University of Athens - BSc
and Chemistry at the University of Thessaloniki - BSc
Mr. Spyridon Fotinos joined Lavipharm in 1979 to establish the plant for drug and cosmetic manufacturing.
In 1987, he established the Research and Development Department, which he has since directed.
His present position in the company is, Executive Vice President - Corporate Research & Innovation
Prior to joining Lavipharm, he served as Director of Planning and Studies at Minerva Pharmaceuticals, (1974-1979)

- Since 1979, he is patentee of several patents reffering to Cosmetic Pharmaceutical - Technology, (Delivery Systems), Antioxidant Systems, and Enzymic Systems.
- He has developed several new pharmaceutical products as well as Cosmetic products (about 100).
- He gives lectures refering to Pharmaceutical developments, to several Universities and Organizations, in Greece and abroad.
- Author of many articles in quite a few scientifically books
- Member of several Greek and International Scientific organizations

Exhibit B

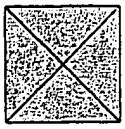
Pharmacological effects of formulations on sexual dysfunction in male subjects having varying etiologies.

etiology (N)	papaverine	PGE[b]	PGE_1[c]	misoprostol[d]	misoprostol[e]	placebo[f]
vascular (N=24)	7	10	5	10	13	0
psychogenic (N=15)	10	11	9	13	14	1
neurogenic (N=5)	2	4	1	4	5	0
hormonal (N=1)	0	1	0	1	1	0
undetermined (N=7)	3	5	1	4	5	1
total (N=52)	22 (42%)	31 (60%)	16 (31%)	32 (62%)	38 (73%)	2 (4%)

The numbers within the boxes indicate those subjects having a positive pharmacological outcome from treatment by the formulation. N indicates the total number of subjects having erectile dysfunction of a particular etiology.

[a] Papaverine (1 ml of 4%) was administered by intracavernosal injection.
[b] PGE_1 0.5 ml of 1.0 mg/ml was administered by intracavernosal injection.
[c] PGE_1 was administered as an ointment (0.1 ml, Macrogol "300" 650 mg, Macrogol "4000" 350 mg), or PGE_1 γ-cyclodextrin complex (corresponding to 1000 μg PGE_1) in 0.1 ml K-Y® jelly for intraurethral use.
[d] Misoprostol (80-100 μg) was administered as an externally applied gel.
[e] Misoprostol (80-100 μg) was administered as an intraurethral applied gel.
[f] Placebo (80-100 μg) was administered an as externally applied gel.

Exhibit C



QUESTION NO.- 1132414.001
ERECTILE DISFUNCTION

Title List

STAY ALERT TO NEW TRENDS
IN YOUR INDUSTRY

Are you staying alert to new developments in your industry?

We can alert you to strategically vital research, journal articles, patents, standards and solutions pertinent to your interests. For more information, call us at 860-872-7000 and speak with one of our scientists or engineers.

DATE- September 15, 2001 QUESTION NO.- 1132414
Technical Specialist- Tammy Aston

TO ORDER DOCUMENTS:

--- Follow this link: http://www.nerac.com/documents
--- Call NERAC Document Services at 860-872-9331
--- Fax your request to 860-875-1749
--- Or send e-mail to documents@nerac.com

Please reference the NDN number of the document(s) you wish to order.
ERECTILE DISFUNCTION BNI ISS 01-38

Citations from B&I - Business and Industry: BNI ISS 01-38

1. NDN 173-0362-5307-6: **MacroChem Drug Failure**
Annotated Title- Stock falls for MacroChem on announcement that an erectile dysfunction medication has failed in tests

1. MacroChem Drug Failure
Annotated Title- Stock falls for MacroChem on announcement that an erectile dysfunction medication has failed in tests

BNI 01-38 03046438 NDN- 173-0362-5307-6

JOURNAL NAME- Wall Street Journal, (3 Star, Eastern (Princeton, NJ) Edition)
VOL. CCXXXVIII
NO. 48
2001-09-07
PAGE- B5
DOCUMENT TYPE- Business Newspaper
JOURNAL CODE- WALLSTRJ
ISSN- 0099-9660
PUBLICATION COUNTRY- United States
SOURCE OF ARTICLE(S)- Business Newspaper
INDUSTRY- Pharmaceutical
LANGUAGE- English

MacroChem Corp's stock fell 47% on the announcement that a drug candidate for treating erectile dysfunction failed. The drug, Topiglan, will be subjected to further study. The brief article offers the company's explanation for the drug's failure.

Question Number: 1132414.001 File: BNI Strategy Date: 07/24/01

NUMBER OF HITS: 1 HIT LIMIT: 25 COPIES: 1

Exhibit D

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

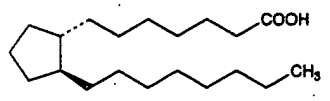
TWELFTH EDITION

Susan Budavari, *Editor*
Maryadele J. O'Neil, *Senior Associate Editor*
Ann Smith, *Associate Editor*
Patricia E. Heckelman, *Assistant Editor*
Joanne F. Kinneary, *Assistant Editor*

Published by
Merck Research Laboratories
Division of
MERCK & CO., INC.
Whitehouse Station, NJ

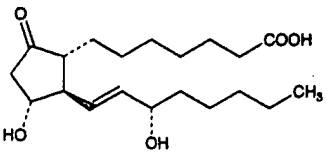
1996

other organs: *idem, Biochim. Biophys. Acta* **84**, 707 (1964). The single non-mammalian source of prostaglandin intermediates, or *syntons*, is the gorgonian sea whip or sea fan, *Plexaura homomalla:* Weinheimer, Spraggins, *Tetrahedron Letters* 1969, 5185; Schneider *et al., J. Am. Chem. Soc.* **94**, 2122 (1972). Prostaglandins are named as derivatives of *prostanoic acid.* Prostaglandins are divided into the types E, F, A, B, C, and D based on functions in the cyclopentane ring. Numerical subscripts refer to the number of unsaturations in the side chains; α or β subscripts refer to the configuration of substituents in the ring. Six naturally occurring prostaglandins, E_1, E_2, E_3, $F_{1\alpha}$, $F_{2\alpha}$, $F_{3\alpha}$, are considered primary in that no one is derived from another in the living organism. First structural and stereochemical elucidations: Bergstrom *et al., Acta Chem. Scand.* **16**, 501 (1962); *eidem, J. Biol. Chem* **238**, 3555 (1963). Absolute config: Nugteren *et al., Nature* **212**, 38 (1966). First total synthesis of racemic PGE_1 and $PGF_{1\alpha}$: Corey *et al., J. Am. Chem. Soc.* **90**, 3245 (1968). Review of synthetic studies: Pike, *Fortschr. Chem. Org. Naturst.* **28**, 313 (1970); Axen *et al.*, in *The Total Synthesis of Natural Products,* **vol. 1**, J. ApSimon, Ed. (Wiley-Interscience, New York, 1973) pp 81-143; Clarkson in *Progress in Organic Chemistry,* **vol. 8**, W. Carruthers, J. K. Sutherland, Eds. (Wiley, New York, 1973) pp 1-28. Book: J. S. Bindra, R. Bindra, *Prostaglandin Synthesis* (Academic Press, New York, 1977). Biosynthesis occurs by enzymatic conversion of unsaturated twenty-carbon fatty acids. Review of biosynthetic studies: Samuelsson, *Progr. Biochem. Pharmacol.* **5**, 109 (1969). Review of metabolism: Samuelsson *et al., Ann. N.Y. Acad. Sci.* **180**, 138 (1971). Biological activities include stimulation of smooth muscle, dilation of small arteries, bronchial dilation, lowering of blood pressure, inhibition of gastric secretion, of lipolysis, and of platelet aggregation, induction of labor, abortion, and menstruation, and increase in ocular pressure. Implicated also in dysmenorrhea, inflammatory reactions, nasal vasoconstriction, kidney function, and in autonomic neuroiransmission. Reviews of pharmacological and biochemical aspects: Horton, *Experientia* **21**, 113 (1965); Weeks, *Ann. Rev. Pharmacol.* **12**, 317 (1972); Hinman, *Ann. Rev. Biochem.* **41**, 161 (1972). Review of biological activities of synthetic prostaglandins: Ramwell *et al., Nature* **221**, 1251 (1969). Review of analytical and preparative techniques: *Methods Enzymol.* **86**, entitled "Prostaglandins and Arachidonate Metabolites", W. E. M. Landis, W. L. Smith, Eds. (Academic Press, New York, 1982) 705 pp. General reviews: Bergstrom, *Science* **157**, 382 (1967); Bergstrom *et al, Pharmacol. Rev.* **20**, 1 (1968); Ramwell, Shaw, *Recent Progr. Horm. Res.* **26**, 139 (1970); Pike, *Sci. Amer.* **225**, 84 (Nov., 1971); Bindra, Bindra, *Progress in Drug Research,* vol. 17 (Birkhäuser Verlag, Basel, 1973) pp 410-487. Books: *The Prostaglandins,* **vols. 1, 2**, P. Ramwell, Ed. (Plenum Press, New York, 1973, 1974); *Prostaglandins in Cardiovascular and Renal Function,* A. Scriabine *et al.,* Eds. (Spectrum Publications, New York, 1980) 498 pp; *Cardiovascular Pharmacology of the Prostaglandins,* A. Herman, Ed. (Raven Press, New York, 1982) 472 pp.



Prostanoic acid

8063. **Prostaglandin E_1.** *(11α,13E,15S)-11,15-Dihydroxy-9-oxoprost-13-en-1-oic acid; 3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentaneheptanoic acid;* alprostadil; PGE_1; U-10136; Caverject; Liple; Minprog; Palux; Prostandin; Prostine VR; Prostivas. $C_{20}H_{34}O_5$; mol wt 354.49. C 67.77%, H 9.67%, O 22.57%. A primary prostaglandin; easily crystallized from purified biological extracts. Isoln from sheep seminal vesicle tissue, and structure: Bergstrom *et al., Acta Chem. Scand.* **16**, 501 (1962); *eidem, J. Biol. Chem.* 238, 3555 (1963). Enzymic conversion from 8,11,14-eicosatrienoic acid: Nugteren *et al., Rec. Trav. Chim.* **85**, 405 (1966). Synthesis of the *dl*-form: Corey *et al., J. Am. Chem. Soc.* **90**, 3245, 3247 (1968); Schneider *et al., ibid.* 5895; **91**, 5372 (1969); Axen *et al., Chem. Commun.* **1969**, 303; Taub *et al., ibid.* **1970**, 1258; Slates *et al., ibid.* **1972**, 304; Kuo *et al., Tetrahedron Letters* **1972**, 5317; Taub *et al., Tetrahedron* **29**, 1447 (1973); Miyano, Stealey, *Chem. Commun.* **1973**, 180; Finch *et al., J. Org. Chem.* **38**, 4412 (1973). Synthesis of natural form: Corey *et al., J. Am. Chem. Soc.* **91**, 535 (1969); **92**, 2586 (1970); Sih *et al., ibid.* **94**, 3643 (1972); **95**, 1676 (1973); Schaaf, Corey, *J. Org. Chem.* **37**, 2921 (1974); Slates *et al., Tetrahedron* **30**, 819 (1974). Metabolism in guinea pigs: Anggard, Samuelsson, *J. Biol. Chem.* **239**, 4097 (1964). Metabolism in humans: Hamberg, Samuelsson, *ibid.* **246**, 6713 (1971). Review of biological activities: Berti *et al., Progr. Biochem. Pharmacol.* **3**, 110 (1967). Comparative pharmacology with respect to other prostaglandins: Weeks, *Ann. Rev. Pharmacol.* **12**, 317 (1972). Clinical use to maintain patency of ductus arteriosus in neonatal cardiac problems: P. M. Olley *et al., Adv. Prostaglandin Thromboxane Res.* **7**, 913 (1980); J. S. Donahoo *et al., J. Thoracic Cardiovasc. Surg.* **81**, 227 (1981); E. D. Silove *et al., Circulation* **63**, 682 (1981). Use in non-atherosclerotic vasculopathy: D. L. Wooster *et al., J. Am. Med. Assoc.* **245**, 1846 (1981). For general refs *see* Prostaglandins.



Crystals from ethyl acetate + heptane, mp 115-116°. $[\alpha]_{578}$ −61.6° (c = 0.56 in tetrahydrofuran). Easily dehydrated in soln at pHs < 4 or > 8.

THERAP CAT: Vasodilator (peripheral).

8064. **Prostaglandin E_2.** *(5Z,11α,13E,15S)-11,15-Dihydroxy-9-oxoprosta-5,13-dien-1-oic acid; 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid;* dinoprostone; PGE_2; U-12062; Cerviprost; Minprostin E_2; Prepidil; Propess; Prostarmon-E; Prostin E_2. $C_{20}H_{32}O_5$; mol wt 352.47. C 68.15%, H 9.15%, O 22.70%. The most common and most biologically potent of mammalian prostaglandins. Isoln from sheep prostate: S. Bergström, J. Sjövall, **Brit. pat. 851,827;** *eidem,* **U.S. pat. 3,598,858** (1960, 1971); from sheep seminal vesicle tissue: S. Bergström *et al., Acta Chem. Scand.* **16**, 501 (1962). Total synthesis of the *dl*-form: W. P. Schneider, *Chem. Commun.* **1969**, 304; E. J. Corey *et al., J. Am. Chem. Soc.* **91**, 5675 (1969); E. J. Corey *et al., Tetrahedron Letters* **1970**, 307; W. P. Schneider, **Ger. pat. 2,011,-969** (1970 to Upjohn), *C.A.* **74**, 87486n (1971); J. Fried *et al., J. Am. Chem. Soc.* **94**, 4342 (1972). Synthesis of naturally occurring form: E. J. Corey *et al., ibid.* **92**, 397, 2586 (1970); J. B. Heather *et al., Tetrahedron Letters* **1973**, 2313; from *Plexaura homomalla* prostaglandin intermediates: G. L. Bundy *et al., J. Am. Chem. Soc.* **94**, 2123 (1972); W. P. Schneider *et al., Chem. Commun.* **1973**, 254. Biosynthesis: D. A. Van Dorp *et al., Biochim. Biophys. Acta* **90**, 204 (1964); S. Bergström *et al., ibid.* 207; **Neth. pat. Appl. 6,-505,799** (1965 to Unilever), *C.A.* **65**, 7584h (1966). Metabolism: E. Anggard, B. Samuelsson, *Mem. Soc. Endocrinol.,* no. 14, 107 (1966); M. Hamberg, B. Samuelsson, *J. Biol. Chem.* **246**, 6713 (1971). Several reviews in *Prostaglandin Symp. Worcester Found. Exp. Biol.,* P. Ramwell, Ed. (Interscience, New York, 1968). For general refs *see* Prostaglandins.